Clinical Pharmacology Review of BLA 974325

Date: May 5, 1998

Reviewer: Carol Braun Trapnell, M.D.

Product: DAB$_{389}$IL-2 intravenous infusion (citrate formulation) for the Treatment of Cutaneous T-Cell Lymphoma (CTCL)

Sponsor: Seragen, Inc.

Clinical Pharmacology Studies Submitted to the BLA

The sponsor has submitted results from a number of studies where the pharmacokinetics of DAB$_{389}$IL-2 were evaluated. . Many of these studies were done in patients with and -------these data are not of primary interest for the sought-after indication of CTCL. However, there are three studies submitted which are relevant to the indication being sought by this BLA which are summarized below:

Protocol	Patients	Study Design	N	DAB$_{389}$IL-2 Dose	Route/Schedule
93-04-l 2	Healthy Volunteers	Biocomparability	45	6 µg/kg/day	IV infusion qd x 5 doses, 1 course
92-04-01	CTCL/NHL/ Hodgkin's	Open-Label, Dose-escalation	73	3 - 31 µg/kg/day	IV infusion qd x 5 doses q 3 weeks ≤8 courses
93-04-l 0	CTCL	Double-Blind	71	9 or 18 µg/kg/day	IV infusion qd x 5 doses q 3 weeks ≤8 courses

This review will discuss each study in detail, particularly describing the relevance of each study's results and conclusions to the use of DAB$_{389}$IL-2 for the treatment of CTCL.

Protocol 93-04- 12

This was a randomized, two arm, parallel group, Phase 1 study of 5 daily doses of DAB$_{389}$IL-2 formulated in either a citrate buffer or)uffer. The change in the manufacturing process resulted in an increase in --- purity and specific activity of DAB389IL-2. The objective of this study was to determine if the two formulations were bioequivalent ; this study was needed due to a formulation change in the DAB$_{389}$IL-2 pharmaceutical preparation midway through the DAB$_{389}$IL-2 development program. Healthy adult male and female volunteers who had an anti-DAB389IL-2 titer of c 1 received 5 daily doses of DAB$_{389}$IL-2 of either the citrate or [redacted] buffered infusion solution in the following doses:

DAB$_{389}$I L-2 [redacted] 7.5 µg/kg/day
DAB$_{389}$IL-2 Citrate: 5.8 µg/kg/day

The sponsor stated that the dose selection was based on the *in vivo* pre-clinical comparative data which suggested that, for a given activity dose level, the mass [redacted] dose was greater than the mass citrate dose. This was consistent with product potency evaluation assays showing that the specific activity of the citrate formulation was greater than that of the [redacted] formulated material.

Eligible study subjects were randomized to receive either the [redacted] or citrate buffered DAB$_{389}$IL-2 infusion. Each dose was administered as a 5-minute IV infusion. Timed blood samples being obtained with the first and fifth doses only pre-dose, then 5, 10, 15, 30, 45, 60, 120, 180 and 240 minutes after the completion of the infusion. The study proposed to enroll 10 evaluable subjects per cohort which was felt to give an [redacted] power to detect a [redacted] difference in the pharmacokinetic parameters (no specific parameters to be compared were mentioned). Finally, blood was obtained at baseline and on study day 15 for assessment of anti-DAB$_{389}$IL-2 antibodies.

Results

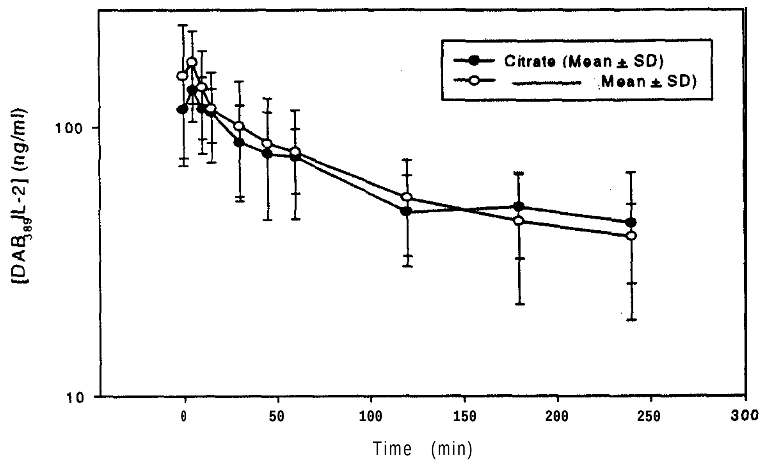
The protocol enrolled 45 subjects in all. This was necessary because, following the enrollment of the first 20 subjects, the sponsor realized there was "a lack of complete documentation of the identity of the formulation prepared or and administered to subjects". Thus, data from the remaining 25 subjects (10 in the citrate group and 15 in the --- group) were evaluable for analysis. All 10 subjects in the citrate group had' blood samples obtained on day 1 of dosing; only 9 subjects have data from day 5 of dosing. In the [redacted] subjects, all 15 subjects have day 1 data, with only 13 subjects having day 5 data. All blood samples were analyzed for DAB$_{389}$IL-2 concentration via both an [redacted] assay and a [redacted].

Evaluation of the DAB$_{389}$IL-2 pharmacokinetic results provided in the submission show that much data are missing. Only 3 subjects have complete sets of data with time points obtained out to the 240 minute sample point. Missing data in the data sets are only noted with a "?" with no further explanation for these missing data provided. Further, in many Instances, there are data for samples analyzed by the -- assay or the [redacted] with missing data (indicated by a

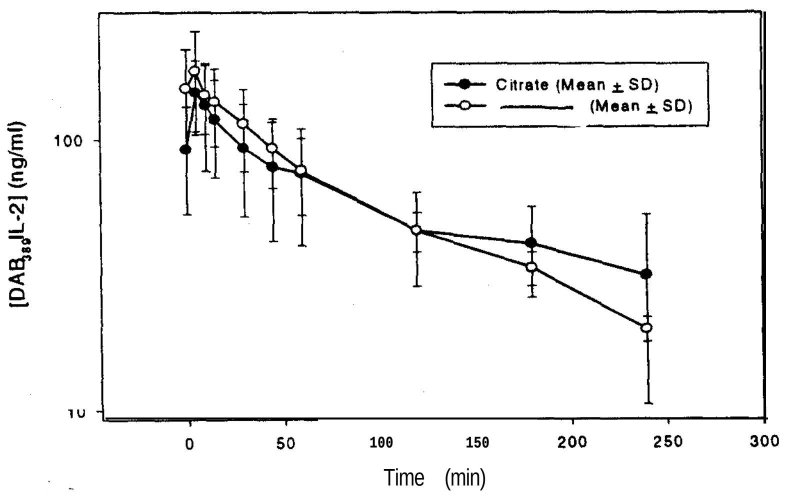
"?") for the other assay used and vice versa; again no explanation for these missing data is provided.

All graphed data below represent mean DAB-IL-2 serum concentrations using **the** — assay; the pharmacokinetic parameters will be discussed using data from both assay methods. These graphs show the concentration vs. time curves for the day 1 and day 5 citrate and — formulation data. It should be noted that the data points are mean values whose overall **"N"** changes with each point, depending on which patients had data available at any given time point.

Day 1 of Administration



Day 5 of Administration



The pharmacokinetic parameters are summarized in the following table. It should be noted that it appears that these mean values were generated from pharmacokinetic analyses of available data from all patients: the completeness of the concentration data was, apparently, not considered for the calculations of the pharmacokinetic parameters such as AUC, $t_{1/2}$, Cl, etc.

Analyses Using an ELISA Assay

Formulation	Day	N	Cmax (ng/ml)	Vd (ml/kg)	$t_{1/2}$ (min)	AUC (ng/ml)xmin	Clp (ml/kg x min)
———	1	14	189±90	64±28	51±20	15989±15075	1.10±0.86
Citrate	1	10	139±33	57±12	69±46	13797±10210	0.85±0.58
———	5	13	173±55	63±18	58±21	14381±6357	0.84±0.41
Citrate	5	8	150±45	53±14	60±28	12840±7839	0.80±0.51

Analyses Using the Bioassay

Formulation	Day	N	Cmax (kU/ml)	Vd (ml/kg)	$t_{1/2}$ (min)	AUC (kU/ml)xmin	Clp (ml/kg x min)
———	1	8	7.3±2.8	29±18	60±11	735±234	0.26±0.10
Citrate	1	2	8.7±0.5	22±1	70±3	1017±188	0.20±0.04
———	5	12	9.6±2.7*	20±7*	61±16	971±353	.020±0.06
Citrate	5	6	7.0±1.7*	29±8*	61±23	733±351	0.36±0.27

*$p \leq 0.05$; statistical test used not clearly identified in the submission

Antibody Formation

As previously stated in this review, only subjects with baseline $DAB_{389}IL$-2 antibody of ≤ 1:5 titers were eligible for the study. Both baseline and day 15 data was available on 22 of the study subjects. It should be noted that 21 of these subjects developed antibodies at dilutions of 1:25, with many subjects developing much higher antibody titers. There was no difference seen in antibody formation between the two formulations.

Conclusions from Protocol 93-04-l 2

The sponsor concluded from this study that the ——— and citrate $DAB_{389}IL$-2 formulations were comparable both clinically and pharmacokinetically when doses were adjusted for the difference in specific activity of the formulations.

The quality of the data submitted in this study prevent the reviewer from reaching the conclusion that the ——— and citrate formulations of $DAB_{389}IL$-2 are bioequivalent when doses are adjusted for activity. The incompleteness of the individual patient data sets are significant. Only 3 patients in each cohort have $DAB_{389}IL\text{-}2$ concentration data out to 240 minutes. The data missing from the study is indicated only by a "?" in the individual data listings without further explanation or clarification leave this study very underpowered to reach the conclusion that the two formulations are comparable.

In addition, this study required subject enrollment twice due to inadequate documentation of study doses by the study site. This certainly raises significant questions on the overall integrity of the study data, particularly in the face of so many missing data points.

These data do, however, suggest that the citrate and ———— formulations may be comparable when dose adjustments are made for their individual activities, but another study to reach this definitive conclusion is required.

Protocol 92-04-01

This was a phase 1, dose ranging, placebo controlled study to determine the pharmacokinetics of $DAB_{389}IL\text{-}2$ in patients with IL-2R expressing lymphoma. The sponsor stated that an objective of this study was to determine if the present of IL-2R receptors seen in these patients would alter the pharmacokinetic profile of DAB&L-2. $DAB_{389}IL\text{-}2$ was administered as a 5-15 minute intravenous infusion for five consecutive days at doses of 3, 6, 9, 12, 15, 19, 23, 27 and 31 μg/kg. It is not clear from the submission how these particular doses were chosen for this study. Blood was obtained from patients at 4 of the nine study sites pre-dose, then 5, 10, 15, 30, 45, 60, 120, 180 and 240 after dosing on Course 1 Day 1 and Course 1 Day 5. Four patients in each dosing tier received $DAB_{389}IL\text{-}2$ with 2 additional patients receiving placebo. In addition, three patients had blood collected for determination of $DAB_{389}IL\text{-}2$ concentrations on Course 3 Day 1 and Course 3 Day 5. Samples were analyzed using both a bioassay as well as an ELISA assay: only the ELISA results will be discussed in this review. The sponsor calculated pharmacokinetic parameters associated with the clearance of $DAB_{389}IL\text{-}2$. Only individuals with detectable serum concentrations at -or more time points and whose data fit a standard one- or two-compartment pharmacokinetic model were included in the pharmacokinetic analyses.

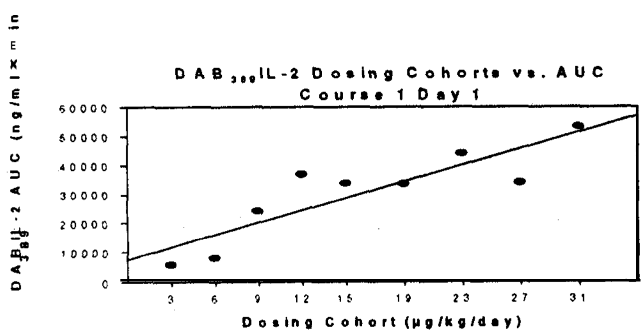
It should be noted that the ———— buff ered formulation of $DAB_{389}IL\text{-}2$ was used in this study. The sponsor notes in the report, "All dose levels are reported as the equivalent mass of citrate formulated $DAB_{389}IL\text{-}2$ as determined by ————

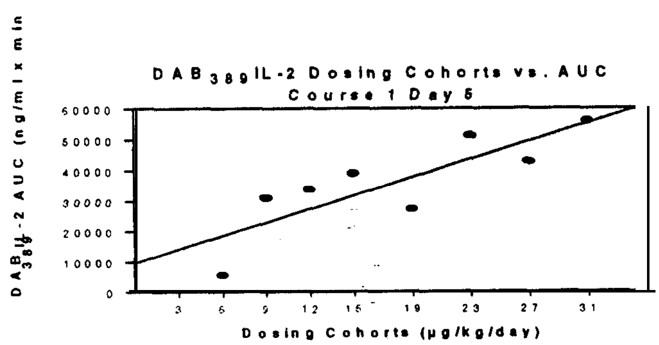
Pharmacokinetic Results

The sponsor stated that partial exclusion of the pharmacokinetic occurred in 5 of the 36 study patients either due to data sets which did not have measurable serum concentrations or because the data did not fit a standard one- or two-compartment model. Further, the sponsor also chose to exclude 4 additional patients from the ______ results because their individual AUC values were less than ___ of the mean AUC value for a particular dose group. Reasons for these variations in results were hypothesized to be " . . . ______________________ ______________ . . ."

Despite these exclusions, the data support the conclusion that $DAB_{389}IL-2$ concentrations increase linearly with the increasing doses administered during Course 1. $DAB_{389}IL-2$ elimination appears to follow a first order process, as the values for clearance and $t_{1/2}$ remained reasonable constant within all of the dosing cohorts.

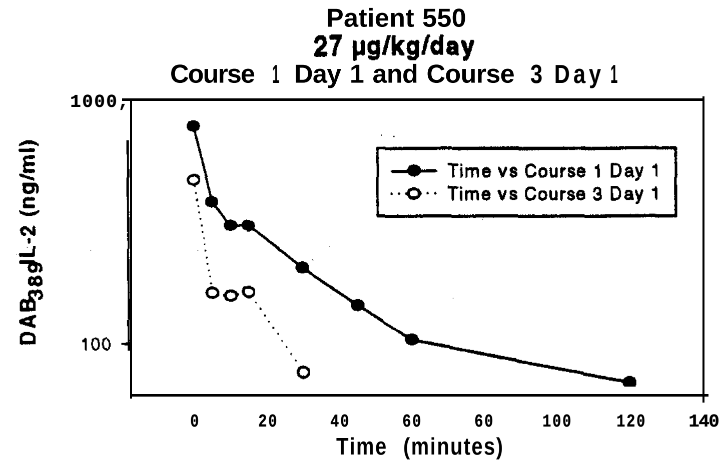
The graphs shown below are regression analyses of the mean AUC values versus the $DAB_{389}IL-2$ dosing cohorts for the pharmacokinetic data obtained on Course 1 Day 1 and Course 1 Day 5. These data show that the increases in AUC appear reasonably constant between doses and there are no changes seen between the values obtained on the two study days, leading to the conclusion that no accumulation of $DAB_{389}IL-2$ is occurring during a 5 day course of treatment.

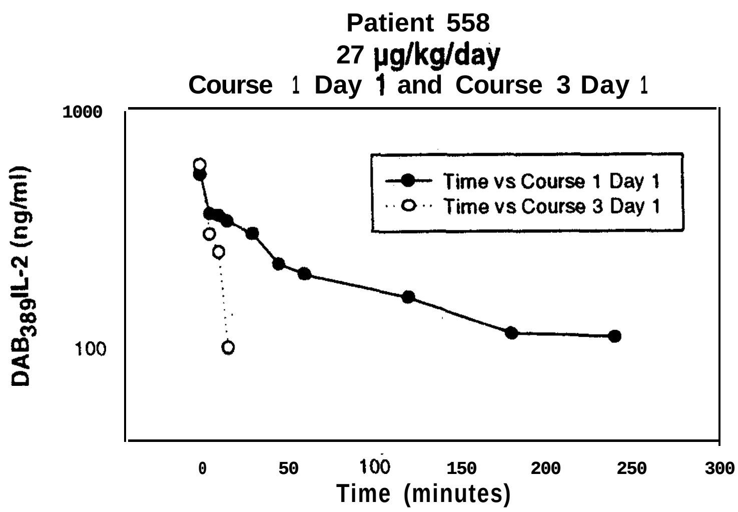




One additional finding that is of particular interest in this study, especially with the pharmacokinetic findings in the Phase 3 study described later in this review, are the pharmacokinetic data obtained in the 3 patients who had $DAB_{389}IL$-2 concentrations determination both during Course 1 and Course 3 of therapy.

The two graphs below show the $DAB_{389}IL$-2 concentration versus time data for two patients, 550 and 558 each of whom received $DAB_{389}IL$-2 27 µg/kg/day, from Day 1 of Courses 1 and 3. The data for the third patient (number 136, who received 31 µg/kg/day) show similar findings





All three patients with repeat DAB$_{389}$IL-2 concentration determinations developed significant anti-DAB$_{389}$IL-2 antibodies by the 3rd course of therapy, which accounts for theses findings. These data provide clear evidence that anti-DAB$_{389}$IL-2 antibody formation has a profound effect on the DAB$_{389}$IL-2 concentrations, and in turn, the pharmacokinetic properties of this product.

Conclusions from Protocol 92-04-01

The data from this study show that, with one 5 day course of therapy, DAB$_{389}$IL-2 display a first order elimination profile with DAB$_{389}$IL-2 exposure increasing in proportion to the increasing doses. However, this study provides the first clue that there is a significant antibody response to this therapy, which, by Course 3, resulted in a significant alteration in the pharmacokinetic profile of DAB$_{389}$IL-2. However, despite these findings, the sponsor apparently chose to proceed with the Phase 3 study in CTCL patients as described below. It is not clear from the BLA submission what attention was paid to the effect of anti-DAB389IL-2 antibody formation on the clinical development plan for DAB$_{389}$IL-2.. It is also not clear from these data how the doses for the Phase 3 study were chosen, as there, again, is no explanation or discussion provided in the BLA as to what DAB$_{389}$IL-2 doses, concentrations and/or exposures were being targeted as possibly effective doses for the CTCL patient population.

As noted above, this study dosed patients with DAB$_{389}$IL-2 buffered in [redacted] and a comment is made in the report that all doses were converted to the citrate equivalent. This statement is presuming pharmacokinetic comparability between the two formulations when the dose is adjusted. It is assumed by the reviewer that the sponsor based this decision of the results of the bioequivalence trial described earlier in this review. However, the data from that trial, as already discussed, do not permit a firm conclusion regarding the dose-adjusted equivalence of these two formulations. However, given that the pivotal, phase 3 trial used only the citrate buffered DAB$_{389}$IL-2 formulation, it is the opinion of the reviewer that this question of equivalence is of no clinical relevance to the use of DAB$_{389}$IL-2 in CTCL patients.

Finally, there were insufficient data to reach a conclusion regarding any relationship between DAB$_{389}$IL-2 pharmacokinetics and the presence of IL-2R receptors as there were two few patients in this study with circulating IL-2R expressing malignant cells to allow for such analyses.

Protocol 93-04-10

> *Reviewer's Comments: This is the most relevant of the studies with clinical pharmacokinetic data due to the fact that the citrate formulation was the sole product used in this trial and it is the first trial where significant numbers of patients receive repeated courses of $DAB_{389}IL\text{-}2$ with assessment of $DAB_{389}IL\text{-}2$ pharmacokinetics during Course 1 and Course 3.*
>
> *It also must be emphasized that the-rationale for the choice of the two dosing regimens in this study, i.e., 9 µg/kg/day and 18 µg/kg/day, are not discussed in the BLA nor does there appear to be data to support the choice of these doses for evaluation of efficacy in this patient population.*

This study was a randomized, double blind, two arm study of $DAB_{389}IL\text{-}2$ in patients with CTCL. Study patients received $DAB_{389}IL\text{-}2$ at either 9 or 18 µg/kg daily as an IV infusion over 15-60 minutes for 5 days; dosing regimens were repeated every 3 weeks. Study patients were permitted to receive up to 10 cycles of $DAB_{389}IL\text{-}2$ given as stated. Blood was obtained on 10 patients in the 9 µg/kg/day cohort and 9 patients in the 18 µg/kg/day cohort during the first and last days of the first and third courses (Course 1 Day 1, Course 1 Day 5, Course 3 day 1 and Course 3 Day 5). Sampling occurred just prior to dosing, then 5, 10, 20, 30, 45, 60, 90, 120. 180 and 240 minutes after the start of the $DAB_{389}IL\text{-}2$ infusion. Blood samples were also obtained in additional patients (21 in the 9 µg/kg/day and 25 in the 18 µg/kg/day dosing groups) 10, 20, 30 and 60 minutes after the start of dosing with these same courses. In addition, blood samples were also obtained on all study patients on day 1 of each course for anti-$DAB_{389}IL\text{-}2$ antibody titers.

The citrate formulation of $DAB_{389}IL\text{-}2$ was the only product administered in this study. All serum $DAB_{389}IL\text{-}2$ concentrations were determined using an ELISA assay. The lower limit of quantitation of this assay was ______ Anti$DAB_{389}IL\text{-}2$ antibodies were determined using an ELISA assay with analyses for $DAB_{389}IL\text{-}2$ neutralizing antibodies determined by an ______ assay which measured the ability of the antibodies to ______ by DAB&L-2. One neutralizing unit was defined as the ______ of $DAB_{389}IL\text{-}2$ or ______ µg. The range of these assay used was for neutralization of clinical samples containing ______ of $DAB_{389}IL\text{-}2$.

The analysis of the pharmacokinetic data was via population estimates for pharmacokinetic parameters associated with clearance of $DAB_{389}IL\text{-}2$ based upon serum concentration versus time data for patients for whom full pharmacokinetic sampling was available. Bayesian analysis, based upon population means were used to generate pharmacokinetic parameters for the patients with partial sampling data. The sponsor noted that data sets were not evaluated for pharmacokinetic parameters if serum concentrations continued to increase well beyond the indicated end of infusion and therefore did not fit the two compartment mathematical model used. In addition, data sets with only one or two time points available were not evaluated.

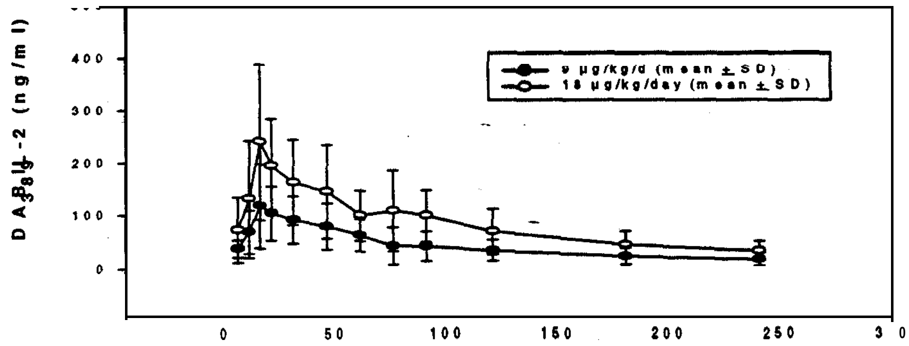
Study Results from the Clinical Pharmacology Perspective

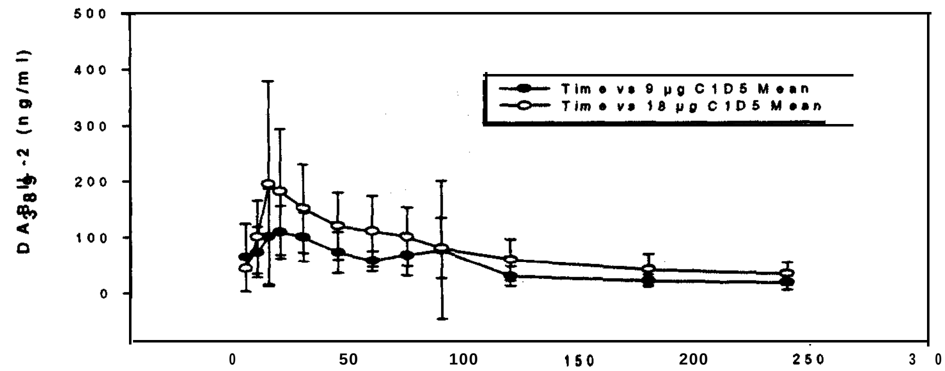
Pharmacokinetics

The pharmacokinetics of DAB&L-2 are quite dependent on the presence of serum antibodies to DAB&L-2. When assessing the pharmacokinetic parameters between the 9 and 18 μg/kg/day doses from Course 1 on Days 1 and 5, it is possible to conclude that the pharmacokinetics of DAB_{389}IL-2 are, indeed, dose proportional as determined by AUC and, the $t_{1/2}$ and Cl values are indicative of a first-order elimination process. These findings are similar to what was seen in the Phase 1/2 study discussed earlier in this review.

The graphs below represent the DAB389IL-2 serum concentration versus time curves comparing the 9 μg/kg/day and 18 μg/kg/day doses given as Course 1, day 1, (C1D1) and Course 1 Day 5 (C1D5):

9 µg/kg versus 18 µg/kg
Course 1
Dayo 1 and 5





The following table lists the pharmacokinetic parameters (mean ± SD) as determined with doses 1 and 5 of the first course of treatment for both dosing cohorts. Despite the variability in these parameters between subjects, as indicated by the fairly large standard deviations, it does appear that the pharmacokinetic parameters change in proportion to the two doses. There is an approximate15 - 2.0 fold increase in the AUC and Cmax for the 18 µg/kg/day, dose, both at days 1 and 5, when compared to the 9 µg/kg/day dose, without significant changes in the $t_{1/2}$ or Cl parameters.

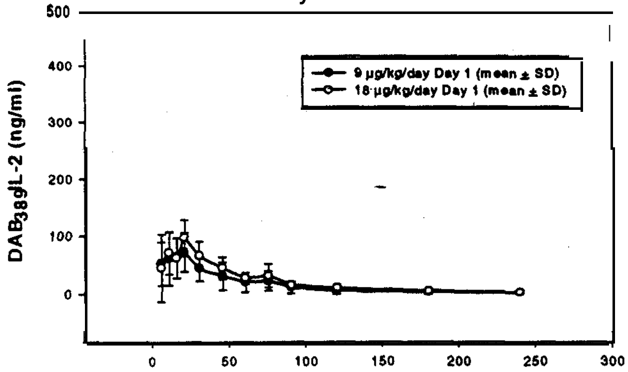
Pharmacokinetic Parameters (mean ± SD) for Course 1 of $DAB_{389}IL-2$ Therapy

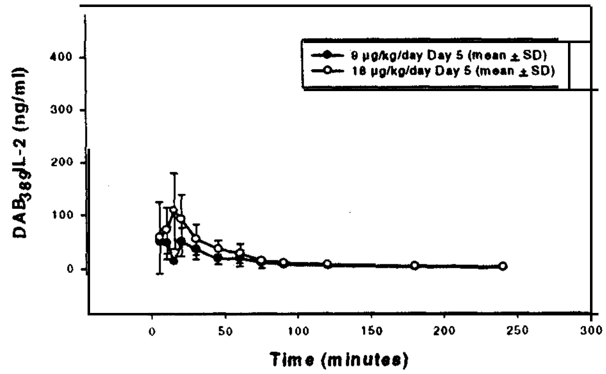
	Course 1 Day 1		Course 1 Day 5	
Parameter	9 µg/kg/day (N=28)	18 µg/kg/day (N=31)	9 µg/kg/day (N=28)	18 µg/kg/day (N=31)
Cmax (ng/ml)	141 ± 114	196 ± 98	147 ± 105	186 ± 94
AUC (ng/ml x min)	11306 ± 7765	15695 ± 13527	10021 ± 4553	14950 ± 8123
Vd (ml/kg)	57 ± 19	83 ± 63	47 ± 13	88 ± 99
$t_{½}$ (min)	82 ± 60	71 ± 71	68 ± 25	72 ± 72
Cl (ml/kg x min)	1.56 ± 1.82	2.04 ± t.63	1.09 ± 0.52	1.59 ± 0.90

However, what is seen in this study is that, following the first and subsequent courses of $DAB_{389}IL-2$ treatment in these CTCL patients, there is a significant antibody response. The BLA states that, after a single course of $DAB_{389}IL-2$, 84% of the patients in this study (41 out of 49) had developed anti-$DAB_{389}IL-2$ antibodies. Following the completion of two courses, every patient in this study except one (patient 0518) had developed anti=$DAB_{389}IL-2$ antibodies. There were no apparent qualitative differences between the two dose groups with respect to the timing or magnitude of anti-DAB&L-2 antibody development, i.e., after the initial treatment with $DAB_{389}IL-2$, the majority of patients developed moderate levels of antibodies which did not change over time with repeated dosing.

The effect of this significant antibody formation is seen very clearly in the $DAB_{389}IL-2$ serum concentration values and the pharmacokinetic parameters obtained with doses 1 and 5 of treatment course 3. The serum concentration versus time curves for these courses are shown below in the following graphs. These graphs show mean (±SD) DAB389IL-2 serum concentration versus time curves comparing the 9 µg/kg/day and 18 µg/kg/day doses given as Course 3, day 1, (C3D1) and Course 3 Day 5 (C3D5):

9 µg/kg vs. 15 µg/kg
Course 3
Days 1 and 5



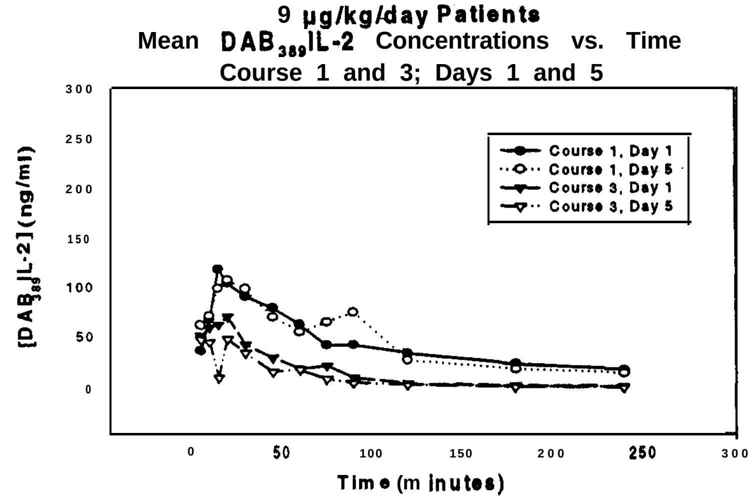


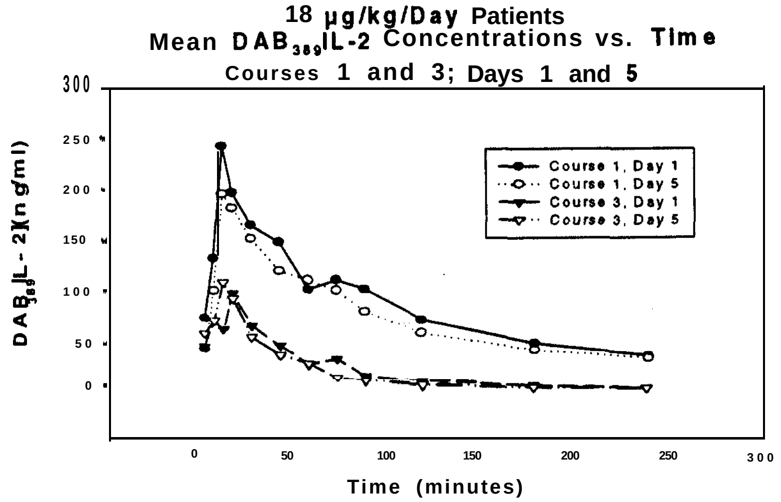
The pharmacokinetic parameters which correspond to these data are shown in the table below:

Pharmacokinetic Parameters (mean ± SD) for Course 3 of $DAB_{389}IL\text{-}2$ Therapy

	Course I Day 1		Course 3 Day 5	
Parameter	9 µg/kg/day (N=28)	18 µg/kg/day (N=31)	9 µg/kg/day (N=28)	18 µg/kg/day (N=31)
Cmax (ng/ml)	89 ± 55	101 ± 29	76 ± 66	90 ± 43
AUC (ng/ml x min)	2985 ± 1689	4877 ± 2554	2226 ± 1266	3518 ± 1541
Vd (ml/kg)	86 ± 33	82 ± 20	96 ± 37	94 ± 66
$t_{1/2}$ (min)	44 ± 31	43 f-22	43 ± 36	50 ± 52
Cl (ml/kg x min)	3.97 ± 2.03	4.39 ± 1.74	6.03 ± 4.80	7.08 ± 6.36

Finally, the concentration versus time graphs from the four sampling periods of the 9 and 18 µg/kg/day $DAB_{389}IL-2$ cohorts, which are the same data shown above but viewed more in toto, are shown below:





These data show, again, that there is a marked reduction in the concentrations of $DAB_{389}IL-2$ during Course 3 of treatment, corresponding to the formation of anti-DAB&L-2 antibodies. The two different doses of $DAB_{389}IL-2$ result in similar exposure to $DAB_{389}IL-2$ by course 3 of treatment. There is essentially no difference seen in the exposures seen between the 9 and 18 µg/kg/day regimens. This, then, creates the effect of a single dose trial, since the anti-DAB$_{389}$IL-2 antibodies result in, essentially, the same quantity of DAB$_{389}$IL-2 present in the serum despite the administration of two distinct doses of this product.

One final observation from the pharmacokinetic data comes from evaluation of the pharmacokinetics for subject 0518, assigned to the 18 µg/kg/day cohort, who did not develop anti-DAB$_{389}$IL-2 antibody titers that were detectable by the ELISA assay methodology after 2 courses of treatment. Evaluation of this patient's data for the duration of the study showed that, in fact, no antibody formation was seen in this patient through 10 courses of treatment (neutralizing anti-DAB&L-2 antibody titers < 0.02 throughout the study). This patient's individual pharmacokinetic parameters assessed with doses 1 and 5 of courses 1 and 3, show the following values

Pharmacokinetic Parameters for Study Patient 0518

Parameter	Course 1 Day 1	Course 1 Day 5	Course 3 Day 1	Course 3 Day 5
Cmax (ng/ml)	61	31	58	78
AUC (ng/ml x min)	7058	4694	5677	3255
Vd (ml/kg)	353	544	134	4*
$t_{1/2}$ (min)	93	99	37	78
Cl (ml/kg x min)	2.55	3.83	3.17	5.53

*Note: The sponsor reported this value of 4 ml/kg; however, in re-computing the pharmacokinetic parameters from the data, the Vd was calculated to be 625 ml/kg. It is assumed by the reviewer that this is a typographical error since all of the other pharmacokinetic parameters in the BLA for this patient agree with the values calculated by the reviewer.

The data from subject 0518 give a hint of the significant degree of intra-individual variability that seems to be present with DAB$_{389}$IL-2 administration. This degree of intra-individual variability can also be seen from review of the pharmacokinetic parameters from course 1 between doses 1 and 5 in all of the patients, where, presumably, no antibodies are yet influencing the pharmacokinetics of DAB&L-2.

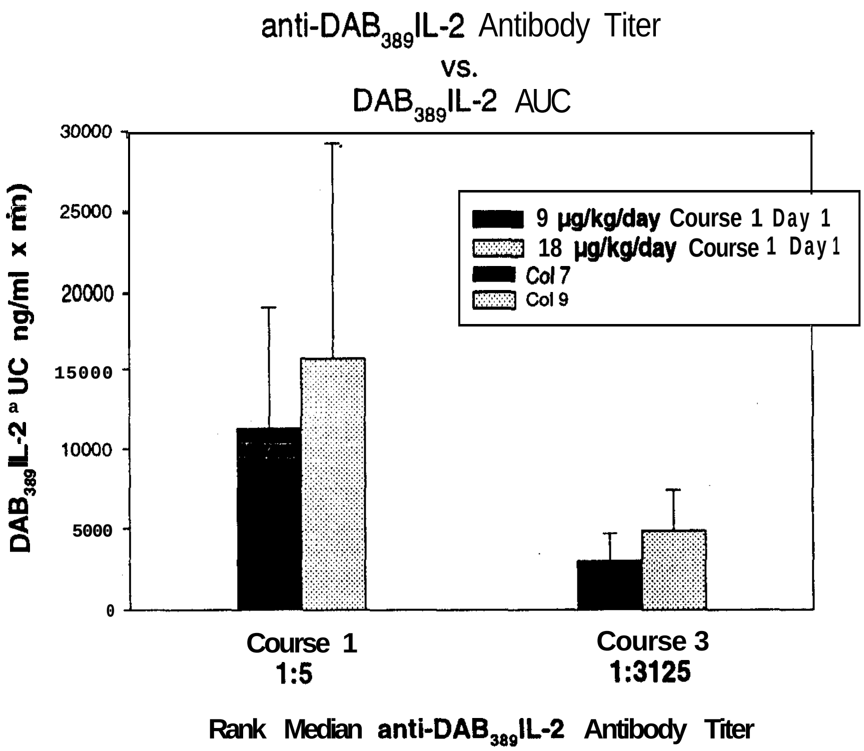
Conclusions of this Study

The pharmacokinetic and pharmacodynamic data from this study provide very valuable information regarding the use and dosing of DAB$_{389}$IL-2 in patients with CTCL. The most striking finding is that the early formation of anti-DAB$_{389}$IL-2 antibodies in nearly 100% of these patients in this study had a profound effect on the $DAB_{389}IL-2$ pharmacokinetics. The Course 1 and Course 3 pharmacokinetic parameters were strikingly different, in that the exposure (as measured by the AUC) was at least ten-fold lower in Course 3 and, further, the clearance of $DAB_{389}IL-2$ increased by at least two-fold from one course to the other. There was clear proportionality in the exposure between the two dosing cohorts in Course 1. However, by Course 3, with the significant degree of anti-$DAB_{389}IL-2$ antibody formation, there was essentially no difference between the exposure or other pharmacokinetic parameters between the two dosing cohorts. This fact makes choosing an optimal "dose" between the two regimens very difficult, as it is not known what concentrations and/or exposures of $DAB_{389}IL-2$ are needed to treat CTCL. Any assessment of $DAB_{389}IL-2$ effectiveness from this study must be combined with these phannacokinetic data. If, for example, the patients who received 18 µg/kg/day had a superior outcome, then it is possible to hypothesize that the initial higher exposures with Course 1 may be responsible for this result. This is particularly true given that $DAB_{389}IL-2$ exposure between the two cohorts becomes virtually identical following the formation of anti-DAB&L-2 antibodies. It is further possible that $DAB_{389}IL-2$ could be administered in higher concentrations as a single course, prior to the formation of any anti-$DAB_{389}IL-2$ antibodies. Again, the outcome data from this clinical study will be critical in assessing the clinical relevance of the changes in $DAB_{389}IL-2$ pharmacokinetics due to anti-DAB&L-2 antibodies

Finally, it would have been interesting to have pharmacokinetic data from later courses of treatment, particularly if correlations could have been attempted between the pharmacokinetics, anti-DAB&L-2 antibody formation and clinical outcomes.

OVERALL CONCLUSIONS OF THE CLINICAL PHARMACOLOGY REVIEW

The results of the pharmacokinetic studies show clearly that the first course of $DAB_{389}IL-2$ produces significant systemic concentrations to this drug and subsequent courses produce concentrations that are both similar and markedly lower despite the administration of two different doses. This abrupt change in the $DAB_{389}IL-2$ dose-exposure relationship appears to be due to the development of anti-DAB&L-2 antibodies. The data presented in this BLA show that, prior to antibody formation, the pharmacokinetics of $DAB_{389}IL-2$ exhibit a first order elimination as determined by clearance and $t_{1/2}$ values that are independent of doses, as well as by dose-proportional increases in $DAB_{389}IL-2$ exposure as measured by AUC and C_{max} values. However, as reported in the BLA, prior to the third course of therapy, nearly 100% of the patients developed antii-$DAB_{389}IL-2$ antibodies which resulted in essentially equivalent drug exposure despite administration of two different doses. These antibodies caused at least a lo-fold reduction in the DAB389IL-2 exposure, compared to the exposure seen with the doses administered during the first course. It is not surprising, then, that, in discussions with the reviewing medical officer, there appear to be no differences in the response rates between the two dosing cohorts studied in the Phase 3 studies. The resultant $DAB_{389}IL-2$ concentrations turn the study comparing the two $DAB_{389}IL-2$ doses into a study, which is, essentially, a single arm trial, given that the two doses yield similar $DAB_{389}IL-2$ concentrations following the first course of treatment. The following graph illustrates this point by comparing median anti-DAB389IL-2 antibody titers to DAB389IL-2 AUC values with both dosing regimens given on day 1 of courses 1 and 3. The median anti-$DAB_{389}IL-2$ antibody titers obtained for both the 9 and 18 µg/kg/day dosing groups were 1:5, obtained prior to Course 1 Dose 1 and 1:3125, obtained just prior to Course 3 Dose 1.



These studies do not discount the possibility that $DAB_{389}IL-2$ may be effective for CTCL. Outcome results from the placebo controlled study which is currently underway would be very helpful in better understanding the role of $DAB_{389}IL-2$ in the treatment of these patients. $DAB_{389}IL-2$ concentrations should also be determined later courses in the treatment regimen to determine if the effects of anti-$DAB_{389}IL-2$ antibodies on $DAB_{389}IL-2$ pharmacokinetics change with continued treatment. Also, a study that compares the administration of maximally tolerated doses of **DAB$_{389}$IL-2** over a short period of time compared to either placebo, standard treatment or the current dosing regimen of 5 day courses given every 3 weeks, could be very informative in understanding the effect of **antiDAB$_{389}$IL-2** antibody formation on the clinical effectiveness of **DAB$_{389}$IL-2** for this indication.

Finally, the issue of product comparability between the [redacted] and citrate formulations of DAB$_{389}$IL-2 is not relevant for this BLA, since-the pivotal study to support the clinical effectiveness claim was done using the citrate formulation. However, the sponsor should be advised that the issue of product comparability may be an issue for the other indications for which **DAB$_{389}$IL-2** is being developed. If this is the case, the current bioequivalence trial submitted with this BLA is inadequate to support a claim of product equivalence for reasons outlined in this review.

Carol Braun Trapnell
Caroll Braun Trapnell, M.D.

Martin D. Green
David Green, Ph.D.

cc: File
Pat Keegan
Bernard Parker
Mercedes Serabian